2-21-97

DATA EVALUATION REPORT

KRESOXIM-METHYL

STUDY TYPE: MULTIGENERATION REPRODUCTION - RAT (83-4)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

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DATA EVALUATION RECORD

STUDY TYPE: Multigeneration Reproduction - Rat
OPPTS 870.3800 [§83-4]

DP BARCODE: D225934 SUBMISSION CODE: S504279
P.C. CODE: 129111 TOX. CHEM. NO.: none

TEST MATERIAL (PURITY): Reg. No. 242 009 (Kresoxim-methyl) (93.7% a.i.)

SYNONYMS: BAS 490F

CITATION: Hellwig, J. (1994) Toxicology Report Reproduction toxicity study with Reg. No. 242 009 (BAS 490 F) in rats: Continuous dietary administration over 2 generations. BASF Aktiengesellschaft, Department of Toxicology, D-67056 Ludwigshafen/Rhine, FRG. BASF Registration Document No. 94/10950, Project No. 70R0180/91093. MRID 43864253. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products Group, P.O. Box 13528, Research Triangle Park, NC 27709-3528.

EXECUTIVE SUMMARY: Reg. No. 242 009 (93.7% a.i.; Lot No. N36 [III c_1]) was administered to groups of 25 male and 25 female Wistar rats in the diet at concentrations of 0, 50, 1000, 4000, or 16,000 ppm for two generations (MRID 43864253). Two litters were produced in the first generation (F_{1a} and F_{1b}) and one litter in the second generation (F_2). Premating doses for the F_0 males were 5.1, 102.6, 411.0, and 1623.1 mg/kg, respectively and for the F_0 females were 5.6, 108.7, 437.2, and 1741.1 mg/kg, respectively. Premating doses for the F_1 males were 4.4, 88.3, 362.7, and 1481.6 mg/kg, respectively, and for the F_1 females were 5.0, 100.8, 416.6, and 1652.6 mg/kg, respectively. Animals were given test or control diet for at least 10 weeks then mated within the same dose group. F_1 animals were chosen from the F_{1a} litters and weaned on the same diet as their parents. At least 22 litters/group were produced in each generation. All animals were exposed to test material either in the diet or during lactation until sacrifice.

There were no dose- or treatment-related clinical signs of toxicity in the parental animals of either sex or generation. Body weights and body weight gains of the F_0 males were

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consistently reduced ($p \leq 0.05$ or 0.01) in the 4000 and 16,000 ppm groups as compared to controls throughout the study with final body weights of these groups 94% and 92%, respectively, of the control value. F_0 females in the 4000 and 16,000 ppm groups had consistently significantly ($p \leq 0.05$ or 0.01) reduced body weights as compared to controls beginning at week 3. Overall body weight gains of the F_0 females were significantly less than the controls in the 4000 ($p \leq 0.05$) and 16,000 ppm ($p \leq 0.01$) groups with final premating body weights 94% and 93%, respectively of the controls.

F_1 males in the high-dose group had significantly ($p \leq 0.01$) lower body weights as compared to controls throughout the entire study with final (week 22) body weights 90% of the control group value. Significantly ($p \leq 0.05$) reduced body weights also occurred in the 4000 ppm males beginning at week 5 and continuing until termination; final body weights were 93% of the controls. Body weight change of the 4000 and 16,000 ppm males was occasionally significantly less than the controls during the first 7 weeks of premating resulting in significantly lower overall (weeks 0-22) body weight gain for these groups as compared to controls. Although absolute body weights of the high-dose F_1 females were significantly ($p \leq 0.05$ or 0.01) less than the controls throughout the premating interval, body weight gains were occasionally less than or greater than the controls. Body weights of the 4000 ppm females were significantly ($p \leq 0.05$) less than the controls at weeks 1-3 and 14. Final premating body weights of the F_1 females in the 4000 and 16,000 ppm groups were 94% and 91%, respectively, of the controls.

Occasional reductions in food consumption of the parental animals of both generations in the 4000 ppm and 16,000 ppm groups did not correspond with reductions in body weights.

Serum γ-glutamyl transferase was significantly increased in F_0 males ($p \leq 0.01$) at ≥4000 ppm and in F_1 males ($p \leq 0.01$) and females ($p \leq 0.05$) at 16,000 ppm. No dose- or treatment-related gross or histological abnormalities were observed at necropsy in either the F_0 or F_1 males or females. There were no statistically significant differences in organ weights of treated groups as compared with controls for the F_0 males or females or the F_1 males. F_1 females in the 4000 and 16,000 ppm groups had significantly ($p \leq 0.05$) lower kidney weights as compared to controls.

Male and female pups of both generations (F_{1a}, F_{1b}, and F_2) from 4000 ppm and 16,000 ppm litters had significantly ($p \leq 0.05$ or 0.01) lower body weights and body weight gains during lactation than the controls. These differences became more pronounced after lactation day 14 when it would be expected that the pups would start to eat the test diets. For the F_{1a} pups there were no significant differences between treated and control groups in physical development. In the F_{1b} litters, the percentage of pups with pinna unfolded by day 4 was significantly less for the 4000

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and 16,000 ppm groups as compared with controls ($p \leq 0.01$ and 0.05, respectively). Eye opening was also delayed ($p \leq 0.05$) in the 4000 ppm F_{1b} pups as compared with controls. At 4000 ppm the F_2 pups had significantly ($p \leq 0.05$) delayed auditory canal opening as compared to controls.

Therefore, the LOEL for systemic/postnatal developmental toxicity is 4000 ppm based on reduced body weights and body weight gains of F_0 and F_1 parental animals and delayed growth and maturation of the F_1 and F_2 pups. The systemic toxicity NOEL is 1000 ppm.

Trends in F_0 and F_1 maternal body weights during gestation and lactation were similar to premating results with significantly ($p \leq 0.05$ or 0.01) lower weights in the 4000 ppm and 16,000 ppm groups. Reductions in food consumption did not correlate with body weight reductions indicating a direct compound-related effect.

No treatment-related effects were observed on the reproductive performances of either generation. There were no dose- or treatment-related clinical signs of toxicity in the offspring of either generation.

Therefore, the NOEL for reproductive toxicity is ≥16,000 ppm and the corresponding LOEL for reproductive toxicity was not identified.

This study is classified as Acceptable and satisfies the guideline requirement for a reproduction study (83-4) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Reg. No. 242 009

   Description: light brown powder
   Lot/Batch No.: N 36 (III c_1)
   Purity: 93.7% a.i.
   Stability of compound: proven stable over the study period
   CAS No.:

2. Vehicle and/or positive control

   Ground Kliba maintenance diet rat/mouse/hamster GLP 343 meal supplied by Klingentalmühle AG, Kaiseraugst, Switzerland was used as vehicle and negative control. No positive control was used in this study.

3. Test animals

Species: rat
Strain: Wistar (Chbb:THOM (SPF))
Age and weight at start of study: 35 ± 1 days; males: 127-158 g, females: 112-140 g
Source: Karl THOMAE, Biberach an der Riss, FRG
Housing: Parental animals were housed individually in type DK III stainless steel wire mesh cages; during mating periods, males were kept individually in Makrolon cages, type M III and females placed into the cages of the males. From GD 18 until lactation day 14, pregnant females and their litters were housed in Makrolon type M III cages. Pregnant females were provided with nesting material.
Diet: Ground Kliba maintenance diet rat/mouse/hamster GLP 343 meal supplied by Klingentalmühle AG, Kaiseraugst, Switzerland was available *ad libitum*.
Water: Tap water was available *ad libitum* from water bottles.
Environmental conditions:
Temperature: 20 - 24°C
Humidity: 30 - 70%
Air Changes: not stated
Photoperiod: 12 hour light/dark
Acclimation period: 7 days

4. Diet preparation and analysis

Fresh diets were prepared at intervals of not more than 32 days. Test diets were prepared by weighing an appropriate amount of test substance and mixing thoroughly with a small amount of food in a Bosch household mixer. An appropriate amount of food was then added to obtain the desired concentration and mixing was carried out for about 10 minutes in a Gebr. Lödige laboratory mixer. Stability and homogeneity of the test mixtures had been previously investigated for a similar batch of test substance in two other rodent studies. Samples from each diet were collected at the beginning of the study and at 3-month intervals for concentration analysis.

Results -
Homogeneity analysis: Results from the analyses of multiple samples taken from diet formulations of 250 and 8000 ppm showed the preparations to be adequately mixed. The variation between samples was less than 3% for all formulations.

Stability analysis: Stability had been previously demonstrated by the testing laboratory for a 50 mg/kg

dietary mixture. The concentration of test substance was 98.4% of the initial concentration after 32 days at ambient temperature.

Concentration analysis: Absence of test article was confirmed in the control diet. Concentrations of test article in the 50, 1000, 4000, and 16,000 mg/kg diets varied 89.0-116%, 91.0-100.3%, 96.5-99.5%, and 93.1-99.1% of nominal, respectively.

Results of the dietary analyses indicated that the test article could be adequately mixed in the diet and that administered concentrations were within 11% of target with the exception of one batch of the 50 ppm diet.

B. STUDY DESIGN

1. In life dates

Start: Sept. 28, 1992; end: Aug. 11, 1993

2. Animal assignment

F_0 animals were randomly assigned to treatment groups according to their body weight three days prior to beginning of treatment. Before weaning, one F_{1a} male and one F_{1a} female were randomly selected from each of 25 litters as the basis of the F_1 parental animals. Where fewer than 25 litters in a group were weaned, the complement was restored by taking a third pup from appropriate litters. F_1 pups were weaned on lactation day 21 onto the same diet as their respective parents. Animal assignment is given in Table 1.

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TABLE 1. Animal assignment

Dose Group	Conc. in Diet[a] (ppm)	No. of Parental animals per group			
		F_0 Generation		F_1 Generation	
		Male	Female	Male	Female
0 (Control)	0	25	25	25	25
1 (Low)	50	25	25	25	25
2 (Mid-1)	1000	25	25	25	25
3 (Mid-2)	4000	25	25	25	25
4 (High)	16,000	25	25	25	25

Data taken from p. 38, MRID 43864253.
[a]Diets were administered from the beginning of the study until the animals were sacrificed.

3. Dose selection rationale

Doses were selected based on the results of several previous studies conducted by the testing facility. Rats were administered Reg. No. 242 009 in the diet at concentrations of 1000, 4000, or 16,000 ppm for 4 weeks. At the high dose (approximately 1455 mg/kg), males had increases in γ-glutamyltransferase and albumin. No effects were seen at the other concentrations or in females at any concentration. In another subchronic study, rats were fed diets containing 500, 2000, 8000, or 16,000 ppm for 3 months. At ≥8000 ppm (approximately 625 or 1272 mg/kg) males had slightly reduced body weights (6-9%) and body weight changes (9-14%), increased γ-glutamyltransferase, and decreased aspartate aminotransferase. Relative liver weights, accompanied by a change in fat distribution, were significantly increased in both sexes at 16,000 ppm and in females at 8000 ppm. A statistically significant increase in relative weights was also seen in females given 2000 ppm (about 159 mg/kg). No treatment-related effects were seen at 500 ppm (about 40 mg/kg).

In a one-generation reproduction toxicity range-finding study, male and female rats were given Reg. No. 242 009 in the diet at concentrations of 4000, 8000, or 16,000 ppm for 6 weeks prior to mating. At the high dose, differences in body weights, serum enzymes, and relative liver weights were similar to the results of the 3 month study. Statistically

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significant growth retardation of the pups occurred at 8000 and 16,000 ppm (approximately 900 and 1800 mg/kg, respectively). Based on the results of these studies, dietary concentrations of 50, 1000, 4000, and 16,000 ppm were chosen for the current study.

C. METHODS

1. Mating procedure and schedule

F_0 animals were fed control or treated diets for at least 70 days prior to mating and continuing throughout mating, gestation, and lactation. At least 10 days after the last weaning of the F_{1a} pups, the F_0 animals were mated again to a different partner to produce the F_{1b} pups. F_1 animals were weaned onto the same diets as were fed their respective parents. The F_{1a} pups were chosen for production of the F_2 generation. After weaning, the F_1 animals were maintained on treatment for at least 98 days prior to mating. For mating, animals of the same dose group were paired overnight one male to one female for a maximum of 3 weeks. Sibling matings were avoided. Females were examined each morning for evidence of mating which consisted of sperm in a vaginal smear. Day 0 of gestation was designated as the day evidence of mating was seen. If a parental animal of either generation did not produced any offspring, it was mated to a proven control animal for not more than 3 weeks for fertility reevaluation.

2. Observation schedule

a. Parental animals

All animals were observed once daily for overt signs of toxicity and mortality. Body weights of the F_0 and F_1 males were recorded weekly throughout the study. Females were weighed weekly until evidence of copulation then on days 0, 7, 14, and 20 of gestation and on days 1, 4, 7, 14, and 21 of lactation. Food consumption for the F_0 and F_1 adults was measured weekly until mating. After mating, food consumption for males was not determined. Food consumption of females was measured for days 0-7, 7-14, and 14-20 during gestation and for days 1-4, 4-7, and 7-14 during lactation. Food consumption was calculated and reported as g/animal/day. Compound consumption was calculated from food consumption and expressed as mg Reg. No. 242 009/kg body weight/day. Group means were determined from the daily intakes of test substance by the individual animals.

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Several days prior to sacrifice, blood was collected from 12 animals/group/sex for clinical chemistry evaluations. Animals were not fasted prior to blood collection. The following enzymes were measured: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and serum-γ-glutamyltransferase.

b. Reproductive performance

The nesting and lactation behavior of the dams was observed once daily and littering behavior was evaluated twice daily on weekdays. The number of days until positive mating for each male and female and the pregnancy status of each female was recorded. The following indices were calculated:

Female fertility index = (No. females pregnant/No. females paired) x 100

Male fertility index = (No. males siring a litter/No. males paired) x 100

Female mating index = (No. females mated/No. females paired) x 100

Male mating index = (No. males confirmed mating/No. males paired) x 100

Gestation index = (No. females with live pups/No. females pregnant) x 100

Live birth index = (No. liveborn pups/No. pups born) x 100

c. Litter observations

All females were allowed to litter normally and the number of live and dead pups was determined. Live pups were sexed at birth and examined once daily for clinical signs and twice daily for mortality or moribundity. Each pup was weighed on lactation days 1, 4 (precull), 7, 14, and 21. On lactation day 4 litters were standardized, where possible, to 4 male and 4 female pups. Selected F_1 pups were weaned on lactation day 21. The following indices were calculated:

Viability index = (No. live pups at lactation day 4 [precull]/No. live pups on day 0) x 100

Lactation index = (No. live pups at lactation day 21/No. live pups on day 4 [postcull]) x 100

Sex ratio = (No. live male or female pups on lactation day 0 or 21/No. live pups on lactation day 0 or 21) x 100

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d. Physical developmental

Pups were examined for completion of the following developmental stages: pinna unfolding by day 4, opening of the auditory canal by day 13, and opening of the eyes by day 15. All surviving pups were tested for gripping reflex (day 13), acoustic startle (day 21), and pupillary reflex (day 20).

3. Postmortem studies

a. Sacrifice

All animals were sacrificed by decapitation while under carbon dioxide anesthesia.

b. Necropsy

1) Parental animals - The F_0 adults were sacrificed following weaning of the F_{1b} pups. The F_1 adults were sacrificed some weeks after weaning of the F_2 pups. A complete necropsy and selective histopathological examination was performed on all animals.

2) Offspring - Offspring dying during lactation were examined for external abnormalities, eviscerated, and their organs assessed grossly. Additional examinations were conducted as deemed appropriate. Pups culled on day 4 and the remaining non-selected pups at day 21 were euthanized and examined grossly. All F_{1b} pups were sacrificed after weaning.

3) Necropsy observations - F_0 and F_1 parental animals were subjected to a gross necropsy consisting of external and internal examinations. The following tissues (X) were preserved in 4% formaldehyde and weighed (XX). Tissues were examined histologically from the control and high-dose groups. Organ and tissue samples from the F_1 and F_2 pups were collected and preserved only as deemed necessary by gross findings.

XX	Testes	X	Ovaries
XX	Epididymides	X	Uterus
X	Prostate	X	Vagina
X	Seminal vesicle	X	Cervix
X	Coagulating gland	X	Oviducts
XX	Liver	X	Pituitary
XX	Kidney	X	Gross lesions

4. Historical control data were included for comparison with concurrent controls.

D. STATISTICAL ANALYSES

Food consumption, body weights and weight changes, number of mating days, duration of gestation, number of pups/litter, and organ weight data were analyzed by Dunnett's test. Reproductive indices and litter data were analyzed by Fisher's Exact test. Pup necropsy data, physical development, and reflex observations were analyzed by the Wilcoxon test. Clinical chemistry values were analyzed by a one-way analysis of variance followed by Dunnett's test to separate means. Statistical significance was set at $p \leq 0.05$ or 0.01.

II. RESULTS

A. SYSTEMIC TOXICITY

1. Mortality and clinical signs

There were no dose- or treatment-related clinical signs of toxicity in the parental animals of either sex or generation.

2. Body weight and food consumption

a. Premating

Body weight and food consumption data for the F_0 males and females are given in Tables 2 and 3, respectively. Body weights of the males were consistently reduced ($p \leq 0.05$ or 0.01) in the 4000 and 16,000 ppm groups as compared to controls throughout the study with final body weights of these groups 94% and 92%, respectively, of the control value. Body weights of the 50 ppm males were occasionally less than the controls, but no significant differences occurred in the 1000 ppm group. Weekly body weight gains were only sporadically significantly different from the controls in the 50 and 1000 ppm groups, whereas weekly body weight gains were consistently reduced ($p \leq 0.05$ or 0.01) in the 4000 and 16,000 ppm groups, especially during the initial premating interval. Body weights of the F_0 females given ≥4000 ppm were also reduced during the first and second premating intervals. Females in the 4000 and 16,000 ppm groups had consistently significantly ($p \leq 0.05$ or 0.01) reduced body weights as compared to controls beginning at week 3 with final premating body weights of these groups 94% and 93%, respectively of the controls.

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The 1000 ppm group females had significantly ($p \leq 0.05$) reduced body weights on weeks 3-6 but recovery was apparent during the remainder of the initial premating period. No significant differences occurred in body weights or body weight gains of the 50 ppm females or in body weight gains of the 1000 ppm group as compared to controls. Overall body weight gains of the F_0 females were significantly less than the controls in the 4000 ($p \leq 0.05$) and 16,000 ppm ($p \leq 0.01$) groups. Food consumption was significantly ($p \leq 0.05$) reduced in the high-dose males for the first week of treatment, but no differences were observed during the remainder of the premating period. In females receiving ≥1000 ppm, food consumption was consistently lower ($p \leq 0.05$ or 0.01) than the controls through about week 5 of the premating interval but was equivalent thereafter.

Body weight and food consumption data for the adult F_1 males and females are given in Tables 4 and 5, respectively. Males in the high-dose group had significantly ($p \leq 0.01$) lower body weights as compared to controls throughout the entire study with final (week 22) body weights 90% of the control group value. Significantly ($p \leq 0.05$) reduced body weights also occurred in the 4000 ppm males beginning at week 5 and continuing until termination; final body weights were 93% of the controls. Weekly body weight gains of the 4000 and 16,000 ppm males were occasionally significantly less than the controls during the first 7 weeks of premating resulting in significantly lower overall (weeks 0-22) body weight gain for these groups as compared to controls. Although absolute body weights of the high-dose F_1 females were significantly ($p \leq 0.05$ or 0.01) less than the controls throughout the premating interval, body weight gains were occasionally less than or greater than the controls. Body weights of the 4000 ppm females were significantly ($p \leq 0.05$) less than the controls at weeks 1-3 and 14. Body weights of the 4000 ppm and 16,000 ppm F_1 females at the end of the premating interval were 94% and 91% of the control value.

High-dose F_1 males had significantly ($p \leq 0.05$ or 0.01) reduced food consumption during premating weeks 1-5. F_1 females in the high-dose group had significantly ($p \leq 0.05$) lower food consumption as compared to controls for weeks 1-2, 2-3, and 4-5. Food consumption for the 4000 ppm group females was significantly ($p \leq 0.05$) less than the

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controls for week 0-1. No other significant differences in food consumption occurred between treated and control groups of either sex during the premating period.

TABLE 2. F_0 Males: Mean body weights and food consumption

Week of study	Treatment Group				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
	Body Weight (g)				
0	143.3 ± 7.55	141.7 ± 6.65	144.0 ± 5.13	142.3 ± 4.90	143.1 ± 6.58
2	248.1 ± 18.45	239.2 ± 14.22	244.4 ± 10.54	240.5 ± 12.70	238.0 ± 12.69*
4	325.9 ± 27.58	310.8 ± 19.52*	314.7 ± 15.78	309.8 ± 21.36*	307.1 ± 18.23**
6	376.1 ± 35.07	358.6 ± 23.84	361.5 ± 20.50	355.2 ± 27.87*	348.8 ± 20.40**
8	418.1 ± 40.81	397.6 ± 24.96	397.1 ± 24.45	392.0 ± 34.89*	384.5 ± 25.97**
10 (end of premating for F_{1a})	449.8 ± 46.48	424.8 ± 28.56*	428.1 ± 27.29	422.1 ± 40.20*	410.9 ± 27.01**
13	475.6 ± 49.62	453.2 ± 27.64	453.4 ± 25.16	447.6 ± 42.52*	432.6 ± 29.31**
16	496.0 ± 54.2	476.8 ± 27.77	477.9 ± 29.38	468.4 ± 47.09	450.3 ± 30.88**
19 (end of premating for F_{1b})	523.0 ± 58.72	504.5 ± 31.92	503.2 ± 33.66	492.8 ± 50.02	477.5 ± 33.76**
29 (end of study)	574.1 ± 67.73	556.5 ± 37.22	554.2 ± 39.87	540.3 ± 56.53	526.4 ± 36.98**
Overall weight gain weeks 0-29	430.8 ± 62.53	414.8 ± 35.20	410.2 ± 39.17	398.0 ± 56.53	383.3 ± 33.4**

TABLE 2. Continued					
Week of study	Treatment group				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Weekly food consumption prior to mating (g/animal/day)					
0-1	25.6 ± 1.48	25.1 ± 1.60	25.9 ± 1.25	25.4 ± 1.74	24.5 ± 1.48*
2-3	29.3 ± 2.16	28.8 ± 1.88	29.7 ± 1.68	29.1 ± 2.20	28.7 ± 1.64
4-5	29.5 ± 2.30	28.2 ± 1.92	29.4 ± 1.48	29.1 ± 2.45	28.7 ± 1.64
6-7	29.1 ± 2.51	28.3 ± 1.47	29.0 ± 1.57	28.6 ± 2.54	27.9 ± 2.06
8-9	29.4 ± 2.97	28.3 ± 1.65	29.2 ± 1.60	28.9 ± 2.89	28.1 ± 1.89
9-10	29.2 ± 2.86	28.0 ± 1.67	28.4 ± 1.69	28.4 ± 2.61	27.9 ± 1.79

Data taken from Tables 1, 7-9, and 12, pp. 128,134-136, and 139, respectively, MRID 43864253.
Significantly different from controls, *$p \leq 0.05$; **$p \leq 0.01$.

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TABLE 3. F_0 Females: Mean body weights and food consumption Prior to mating

Week of study	Treatment group				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Body weight (g)					
0	127.8 ± 4.96	124.9 ± 7.58	125.2 ± 5.60	125.1 ± 5.68	124.2 ± 4.40
1	157.3 ± 8.24	152.9 ± 9.69	152.2 ± 7.98	153.1 ± 7.66	151.6 ± 5.79*
2	179.2 ± 10.30	176.5 ± 12.39	173.0 ± 10.65	174.4 ± 8.97	173.1 ± 7.11
4	213.9 ± 13.94	206.5 ± 13.94	203.9 ± 12.91*	202.4 ± 13.06**	200.0 ± 10.62**
6	239.9 ± 14.84	232.3 ± 18.52	227.7 ± 18.44*	222.7 ± 14.91**	223.2 ± 13.39**
8	258.0 ± 17.83	251.2 ± 21.83	247.4 ± 19.32	242.1 ± 16.30*	241.1 ± 16.76**
10 (end of premating for F_{1a})	271.6 ± 18.31	264.0 ± 24.23	260.2 ± 21.53	254.9 ± 17.25*	253.3 ± 17.30**
Weight gain weeks 0-10	143.8 ± 15.46	139.1 ± 19.15	134.9 ± 18.63	129.9 ± 14.85*	129.1 ± 15.64**
19 (end of premating for F_{1b})	316 ± 17.17	309.2 ± 27.56	303.1 ± 25.55	297.1 ± 21.30*	292.8 ± 20.90**
Food consumption (g/animal/day)					
0-1	21.6 ± 1.28	21.3 ± 1.65	20.8 ± 1.50	20.6 ± 0.99*	19.8 ± 1.13**
2-3	21.9 ± 1.66	21.3 ± 1.74	20.7 ± 1.54*	20.7 ± 1.51*	20.5 ± 1.29**
4-5	22.3 ± 1.41	22.0 ± 1.99	20.8 ± 1.57**	21.2 ± 1.50	21.2 ± 1.43
6-7	21.7 ± 1.46	22.1 ± 2.14	21.6 ± 1.58	21.4 ± 1.58	21.4 ± 1.54
8-9	21.9 ± 1.63	21.9 ± 1.96	21.3 ± 1.65	21.4 ± 1.45	21.5 ± 1.40
9-10	22.0 ± 1.45	21.9 ± 1.83	21.1 ± 1.71	21.1 ± 1.44	21.1 ± 1.33

Data taken from Tables 2, 13, 14, and 19, pp. 129, 140, 141, and 146, respectively, MRID 43864253.
Significantly different from control, *$p \leq 0.05$, **$p \leq 0.01$.

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TABLE 4. F_1 Males: Mean body weights and food consumption

Week of study	Treatment group				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
	Body weight (g)				
0	145.6 ± 13.34	142.7 ± 17.2	143.9 ± 14.03	137.5 ± 19.36	125.0 ± 10.91**
2	253.1 ± 20.03	249.0 ± 27.07	249.5 ± 20.65	239.5 ± 27.72	226.0 ± 15.70**
4	341.9 ± 23.13	334.4 ± 30.62	334.5 ± 22.80	324.0 ± 31.25	308.0 ± 18.49**
8	436.8 ± 35.11	421.4 ± 36.86	422.9 ± 27.52	408.7 ± 36.28**	389.8 ± 22.20**
12	486.9 ± 43.04	472.3 ± 43.57	475.0 ± 31.42	459.5 ± 43.11*	438.5 ± 25.42**
14 (end of premating)	513.4 ± 46.66	497.9 ± 47.04	499.1 ± 35.70	480.6 ± 46.69*	459.9 ± 27.93**
22 (end of study)	566.1 ± 54.07	552.1 ± 52.07	552.0 ± 42.87	527.2 ± 54.17*	506.8 ± 31.99**
Weight gain weeks 0-14[a]	367.8	355.2	355.2	343.1	334.9
Weight gain weeks 0-22	420.5 ± 50.33	409.4 ± 45.61	408.0 ± 36.70	389.7 ± 43.59*	381.8 ± 30.59**

TABLE 4. Continued

Week of Study	Treatment group				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Food consumption prior to mating (g/day) [a]					
0-1	25.0 ± 1.77	25.0 ± 2.45	25.1 ± 1.77	24.7 ± 2.53	23.7 ± 1.55
1-2	28.2 ± 2.38	28.3 ± 2.59	27.9 ± 1.88	27.5 ± 2.79	26.5 ± 1.95*
3-4	30.6 ± 1.77	30.2 ± 2.32	29.9 ± 1.83	30.1 ± 2.58	29.1 ± 1.94*
7-8	30.0 ± 2.43	30.2 ± 2.37	30.1 ± 1.80	29.8 ± 2.29	28.7 ± 1.70
11-12	29.3 ± 2.60	28.9 ± 2.29	28.9 ± 1.81	28.8 ± 2.40	27.8 ± 1.69
13-14	28.7 ± 2.67	28.4 ± 2.37	28.6 ± 3.08	27.7 ± 2.40	27.1 ± 2.20

Data taken from Tables 77-78 and 83-88, pp. 204-205 and 210-215, respectively, MRID 43864253.
[a]Calculated by reviewer from week 0 and 14 group means.
Significantly different from control, *$p \leq 0.05$, **$p \leq 0.01$.

TABLE 5. F_1 Females: Mean body weights and food consumption prior to mating

Week of study	Treatment group				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Body weight (g)					
0	127.0 ± 12.63	124.2 ± 10.66	125.1 ± 11.53	119.7 ± 10.12	114.0 ± 7.69**
2	177.5 ± 14.04	171.7 ± 13.64	173.3 ± 14.10	167.4 ± 11.60*	162.3 ± 9.82**
4	209.4 ± 18.00	206.6 ± 19.41	205.0 ± 16.77	198.1 ± 13.38	193.6 ± 14.40**
8	253.8 ± 20.36	250.5 ± 26.16	249.1 ± 22.07	241.3 ± 16.39	238.6 ± 17.52*
12	278.2 ± 22.29	274.7 ± 28.28	272.7 ± 23.96	262.5 ± 17.96	260.6 ± 20.92*
14	290.4 ± 24.06	283.1 ± 26.37	281.9 ± 28.16	272.2 ± 18.38*	265.2 ± 22.9**
Weight gain weeks 0-14	163.3 ± 20.36	158.9 ± 22.97	156.9 ± 23.3	152.5 ± 17.12	151.2 ± 21.04
Food consumption (g/day)					
0-1	20.1 ± 1.30	19.7 ± 1.45	19.9 ± 1.30	19.1 ± 1.19*	19.4 ± 1.11
1-2	20.7 ± 1.58	20.2 ± 2.09	20.6 ± 1.64	20.4 ± 1.13	19.5 ± 1.83*
3-4	21.4 ± 1.95	21.0 ± 2.48	21.0 ± 1.81	21.2 ± 1.37	20.3 ± 1.90
7-8	22.3 ± 1.53	22.7 ± 2.27	23.0 ± 1.67	23.2 ± 1.67	22.2 ± 1.67
11-12	22.2 ± 1.44	22.1 ± 1.89	22.2 ± 1.63	22.1 ± 1.38	21.7 ± 1.89
13-14	21.0 ± 1.49	21.3 ± 1.66	21.6 ± 2.16	21.0 ± 1.54	20.6 ± 1.94

Data taken from Tables 89-92 and 79-80, pp. 216-219 and 206-207, respectively, MRID 43864253.
Significantly different from control, *$p \leq 0.05$, **$p \leq 0.01$.

b. Gestation and lactation

Body weights, body weight gains, and food consumption data for the F_0 adult females during gestation and lactation of the F_{1a} and F_{1b} litters are given in Table 6. Maternal body weights during gestation of both the F_{1a} and F_{1b} litters were significantly ($p \leq 0.05$ or 0.01) less than the controls in the 4000 ppm group on GD 0, 7, and 14 and in the 16,000 ppm group throughout gestation. Maternal body weights were significantly less than the controls during lactation of the F_{1a} pups in the 1000 ppm group on day 7 ($p \leq 0.05$), in the 4000 ppm group on days 1, 4, and 7 ($p \leq 0.05$), and in the 16,000 ppm group throughout the entire lactation period ($p \leq 0.05$ or 0.01). During lactation of the F_{1b} pups, maternal body weights were significantly less than the controls in the 4000 ppm group on days 1, 4, and 7 and in the 16,000 ppm group on days 1, 4, 7, and 14 ($p \leq 0.05$ or 0.01). There were no significant differences between treated and control groups for body weight gains during gestation of either litter or during lactation of the F_{1a} pups. During lactation of the F_{1b} litters, maternal weight gain was significantly ($p \leq 0.05$) greater than the controls in the 4000 ppm group on days 7-14 and in the high-dose group on days 14-21 and overall.

Maternal food consumption was significantly decreased for the high-dose F_0 animals as compared with controls during gestation days 0-7 ($p \leq 0.01$) and 7-14 ($p \leq 0.05$) and during lactation days 4-7 ($p \leq 0.05$) and 7-14 ($p \leq 0.01$) in production of the F_{1a} litters. However overall food consumption during gestation and lactation of the F_{1a} pups was not significantly different between treated and control groups. No differences occurred in food consumption between treated and control groups during gestation and lactation of the F_{1b} litters.

Maternal body weights, body weight gains, and food consumption data for the F_1 females during gestation and lactation of the F_2 offspring are given in Table 7. Maternal body weights were significantly ($p \leq 0.05$ or 0.01) lower than the controls in the 16,000 ppm group throughout gestation and lactation and in the 4000 ppm group on GD 0, 7, and 14 and lactation days 1, 4, 7, and 14. Body weight gain was significantly ($p \leq 0.05$) less in the high-dose group as compared with controls on GD 0-7. Body weight gains during lactation were significantly greater than the

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controls for the 4000 ppm group on days 7-14, 14-21, and 1-21 and for the 16,000 ppm group on days 14-21 and 1-21. Food consumption for the high-dose group was significantly ($p \leq 0.01$) less than the controls during days 1-7 and 7-14 of gestation. No other significant differences in food consumption occurred between treated and control groups during gestation or lactation.

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TABLE 6. F_0 Females: Selected mean body weights, body weight gains, and food consumption values during gestation and lactation

Observation	Treatment group				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
F_{1a} Generation					
Mean body weight (g)					
Day 0 of gestation	274.6 ± 18.83	264.1 ± 24.58	262.7 ± 22.39	255.0 ± 15.79**	255.0 ± 17.45**
Day 20 of gestation	403.1 ± 23.67	397.1 ± 33.24	387.1 ± 33.55	383.1 ± 24.51	379.7 ± 25.27*
Day 1 of lactation	314.1 ± 14.88	302.1 ± 30.67	300.1 ± 25.69	296.0 ± 18.88*	288.8 ± 18.57**
Day 21 of lactation	334.3 ± 19.87	322.4 ± 26.72	321.8 ± 25.04	322.6 ± 26.29	315.8 ± 17.46*
Mean body weight gain (g)					
Day 0-20 of gestation	128.5 ± 14.06	132.9 ± 14.17	124.4 ± 18.11	128.2 ± 13.61	124.6 ± 15.34
Day 1-21 of lactation	20.2 ± 16.32	20.3 ± 14.17	21.7 ± 11.92	26.6 ± 13.65	26.9 ± 10.68
Mean food consumption (g/animal/day)					
Day 0-20 of gestation	27.5 ± 1.39	27.0 ± 1.44	26.5 ± 1.43	27.1 ± 1.58	26.1 ± 1.86
Day 1-14 of lactation	51.7 ± 12.09	52.1 ± 10.64	50.3 ± 11.22	50.8 ± 11.28	49.0 ± 9.84

TABLE 6. Continued

Observation	Treatment group				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
F_{1b} Generation					
Mean body weight (g)					
Day 0 of gestation	317.9 ± 17.77	310.2 ± 28.50	304.5 ± 26.47	298.2 ± 20.59*	291.0 ± 18.28**
Day 20 of gestation	455.0 ± 27.23	447.0 ± 42.94	441.5 ± 39.40	434.8 ± 30.14	421.9 ± 23.11**
Day 1 of lactation	349.6 ± 20.03	341.1 ± 31.17	335.5 ± 31.52	329.1 ± 25.62*	319.4 ± 21.73**
Day 21 of lactation	369.2 ± 22.26	360.1 ± 26.55	352.2 ± 30.76	358.6 ± 26.42	351.3 ± 21.11
Mean body weight gain (g)					
Day 0-20 of gestation	137.0 ± 19.92	136.8 ± 20.80	136.9 ± 17.37	136.6 ± 17.45	130.9 ± 12.73
Day 1-21 of lactation	19.7 ± 14.63	19.0 ± 14.51	16.7 ± 13.85	29.5 ± 12.29	31.9 ± 12.64*
Mean food consumption (g/animal/day)					
Day 0-20 of gestation	28.4 ± 1.23	28.4 ± 1.48	27.9 ± 1.16	28.1 ± 1.42	27.3 ± 1.49
Day 1-14 of lactation	51.6 ± 11.05	49.9 ± 11.66	49.8 ± 9.81	49.8 ± 10.24	50.0 ± 9.39

Data taken from Tables 3-6, 15-18, and 21-24, pp. 130-133, 142-145, and 148-151, respectively, MRID 43864253.
Significantly different from control, *$p \leq 0.05$; **$p \leq 0.01$.

TABLE 7. F_1 Fmales: Slected mean body weights, body weight gains, and food consumption values during gestation and lactation

Observation	Treatment group				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Mean body weight (g)					
Day 0 of gestation	289.9 ± 20.29	282.3 ± 28.10	282.3 ± 25.11	268.4 ± 17.65**	265.3 ± 21.06**
Day 20 of gestation	411.5 ± 40.15	395.5 ± 40.77	407.3 ± 42.33	394.3 ± 25.66	373.6 ± 40.74**
Day 1 of lactation	332.7 ± 22.03	321.0 ± 28.14	323.7 ± 31.42	307.3 ± 17.93**	298.8 ± 19.56**
Day 21 of lactation	337.7 ± 20.46	327.3 ± 20.86	331.7 ± 23.80	328.3 ± 20.97	320.7 ± 18.98*
Mean body weight gain (g)					
Day 0-20 of gestation	121.7 ± 27.12	113.2 ± 32.51	125.0 ± 29.06	125.9 ± 15.52	108.4 ± 34.76
Day 1-21 of lactation	5.0 ± 14.22	6.3 ± 13.85	8.0 ± 14.20	21.0 ± 9.58**	22.0 ± 11.92**
Mean food consumption (g/animal/day)					
Day 0-20 of gestation	26.2 ± 1.14	25.5 ± 1.04	26.3 ± 1.24	26.0 ± 1.87	24.4 ± 1.38
Day 1-14 of lactation	45.7 ± 12.44	44.0 ± 11.94	44.7 ± 12.26	44.4 ± 11.7	43.6 ± 11.44

Data taken from Tables 81-82 and 93-96, pp. 208-209 and 220-223, respectively, MRID 43864253.
Significantly different from control, *$p \leq 0.05$; **$p \leq 0.01$.

3. Test substance intake

Doses, expressed as mg of test substance/kg body weight/day, during the premating period for males and females and during gestation and lactation for females are presented in Table 8. At no time during the study were the weekly doses from the 16,000 ppm diets below 1000 mg/kg/day for the F_0 males and females or the F_1 females. During weeks 12-13 and 13-14 the test substance doses in the F_1 males receiving 16,000 ppm were 995.5 and 965.6 mg/kg/day, respectively.

TABLE 8: Test substance intake in rats fed kresoxim-methyl for two generations (mg/kg/day)

Sex - Study interval	Concentration in diet			
	50 ppm	1000 ppm	4000 ppm	16,000 ppm
F_0 Generation				
Males -Premating	5.1	102.6	411.0	1623.1
Females - Premating	5.6	108.7	437.2	1741.1
Females - Gestation of F_{1a}	4.6	91.7	383.8	1482.5
Females - Lactation of F_{1a}	8.3	162.0	661.8	2610.5
Females - Gestation of F_{1b}	4.3	84.8	348.9	1389.3
Females - Gestation of F_{1b}	7.1	143.2	587.2	2409.0
F_1 Generation				
Males -Premating	4.4	88.3	362.7	1481.6
Females - Premating	5.0	100.8	416.6	1652.6
Females - Gestation	4.1	84.5	351.1	1349.1
Females - Lactation	6.8	136.4	564.4	2278.8

Data taken from Tables 25-30 and 97-102, pp. 152-157 and 224-229, MRID 43864253.

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4. Clinical chemistry

Results of serum enzyme activities for the adult F_0 and F_1 animals are given in Tables 9 and 10, respectively. Alanine aminotransferase was significantly ($p \leq 0.05$ or 0.01) decreased in F_0 males at ≥1000 ppm, in F_0 females at 16,000 ppm, and in F_1 males and females at ≥4000 ppm. In both sexes of both generations, alkaline phosphatase was significantly decreased at ≥1000 ppm. Serum γ-glutamyl transferase was significantly increased in F_0 males at ≥4000 ppm and in F_1 males and females at 16,000 ppm.

TABLE 9: F_0 Clinical chemistry					
Enzyme	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Males					
Alanine amino transferase (mykat/L)	1.26 ± 0.17	1.21 ± 0.16	1.04 ± 0.12**	1.07 ± 0.20*	0.94 ± 0.20**
Alkaline phosphatase (mykat/L)	5.05 ± 0.66	4.66 ± 0.64	4.04 ± 0.37**	4.14 ± 0.28**	3.89 ± 0.48**
γ-Glutamyltransferase (nakat/L)	0 ± 0	5 ± 10	9 ± 18	41 ± 18**	71 ± 55**
Females					
Alanine amino transferase (mykat/L)	0.98 ± 0.09	0.98 ± 0.14	0.91 ± 0.11	0.93 ± 0.18	0.69 ± 0.10**
Alkaline phosphatase (mykat/L)	3.09 ± 0.55	2.82 ± 0.46	2.45 ± 0.38**	2.30 ± 0.43**	2.51 ± 0.38**
γ-Glutamyltransferase (nakat/L)	1 ± 4	0 ± 0	3 ± 6	8 ± 12	11 ± 17

Data taken from Tables 125 and 126, pp. 252 and 253, respectively, MRID 43864253.
Significantly different from control: *p ≤ 0.05, **p ≤ 0.01.

TABLE 10: F_1 Clinical chemistry					
Enzyme	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Males					
Alanine amino transferase (mykat/L)	1.17 ± 0.30	0.97 ± 0.18	0.99 ± 0.17	0.94 ± 0.21*	0.78 ± 0.06**
Alkaline phosphatase (mykat/L)	5.23 ± 0.80	4.72 ± 1.03	3.97 ± 0.58**	3.72 ± 0.65**	3.87 ± 0.34**
γ-Glutamyltransferase (nakat/L)	9 ± 12	15 ± 35	6 ± 8	30 ± 13	102 ± 42**
Females					
Alanine amino transferase (mykat/L)	1.00 ± 0.23	1.00 ± 0.20	0.87 ± 0.11	0.81 ± 0.10*	0.72 ± 0.09**
Alkaline phosphatase (mykat/L)	4.06 ± 0.90	4.01 ± 0.66	3.30 ± 0.45*	3.11 ± 0.38**	3.39 ± 0.60*
γ-Glutamyltransferase (nakat/L)	0 ± 0	0 ± 0	4 ± 13	10 ± 18	16 ± 17*

Data taken from Tables 127 and 128, pp. 254 and 255, respectively, MRID 43864253.
Significantly different from control: *p ≤ 0.05, **p ≤ 0.01.

5. Necropsy results

a. Organ weights

There were no statistically significant differences in organ weights of treated groups as compared with controls for the F_0 males or females or the F_1 males. F_1 females in the 4000 and 16,000 ppm groups had significantly ($p \leq 0.05$) lower kidney weights as compared to controls.

b. Pathology

1) Gross pathology - No dose- or treatment-related gross abnormalities were observed in either the F_0 or F_1 males or females.

2) Microscopic pathology - No dose- or treatment-related histological abnormalities were observed for either sex or generation. Common findings in both generations of treated and control groups were fatty infiltration of the liver in males and focal calcification of the kidneys in females. The incidence and severity of fatty infiltration of the liver in males decreased slightly with increasing dose.

B. REPRODUCTIVE TOXICITY

1. Reproductive performance

The reproductive performances of the F_0 animals are summarized in Tables 11 and 12 and of the F_1 animals in Table 13. No treatment-related effects were observed on the reproductive performances of either generation. The fertility indices for the F_0 males and females receiving 4000 ppm were slightly less than the controls for production of the F_{1a} litters but were similar to controls for production of the F_{1b} litters.

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TABLE 11. F_0 Generation reproductive performance for production of the F_{1a} litters

Observation	Dietary concentration				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Mean nights to positive mating	2.6	2.2	2.2	2.2	2.8
Males					
Number paired	25	25	25	25	25
Number siring	25	23	25	22	24
Females					
Number paired	25	25	25	25	25
Number pregnant	25	23	25	22	24
Number delivering	25	23	25	22	24
Indices (%)					
Male mating index	100	100	100	100	100
Male fertility index	100	92	100	88	96
Female mating index	100	100	100	100	100
Female fertility index	100	92	100	88	96
Mean gestation length (days)	22.0	22.0	21.9	21.9	21.8

Data taken from Tables 46 and 48, pp. 173 and 175, respectively, MRID 43864253.

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TABLE 12. F_0 Generation reproductive performance
For production of the F_{1b} litters

Observation	Dietary concentration				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Mean nights to positive mating	2.9	3.0	2.4	1.9	2.7
Males					
Number paired	25	25	25	25	25
Number siring	25	24	25	23	24
Females					
Number paired	25	25	25	25	25
Number pregnant	25	24	25	23	24
Number delivering	25	24	25	23	24
Indices (%)					
Male mating index	100	100	100	100	100
Male fertility index	100	96	100	92	96
Female mating index	100	100	100	100	100
Female fertility index	100	96	100	92	96
Mean gestation length (days)	22.0	21.8	21.8	21.7	21.8

Data taken from Tables 47 and 49, pp. 174 and 176, respectively, MRID 43864253.

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TABLE 13. F_1 generation reproductive performance for production of the F_2 litters

Observation	Dietary concentration				
	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Mean nights to positive mating	2.3	2.6	2.7	2.3	2.6
Males					
Number paired	25	25	25	25	25
Number siring	24	22	24	25	23
Females					
Number paired	25	25	25	25	25
Number pregnant	24	22	24	25	23
Number delivering	24	22	24	25	23
Indices (%)					
Male mating index	100	100	100	100	100
Male fertility index	96	88	96	100	92
Female mating index	100	100	100	100	100
Female fertility index	96	88	96	100	92
Mean gestation length (days)	22.1	22.2	22.1	22.0	22.0

Data taken from Tables 109 and 110, pp. 236 and 237, respectively, MRID 43864253.

2. Viability and clinical signs

Viability data of the F_{1a}, F_{1b}, and F_2 litters are given in Tables 14, 15, and 16, respectively. There were no dose- or treatment-related clinical signs of toxicity in the offspring of either generation. Pup survival was similar between treated and control groups of both generations.

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TABLE 14: Viability of F_{1a} litters during lactation

Observation/ study time	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Number of litters	25	23	25	22	24
Total number of pups	350	357	340	304	329
Number of pups born alive	343	343	332	299	319
Number of pups still born	7	14	8	5	10
Sex ratio (% male)	52.8	53.4	48.8	55.5	52.0
Mean number live pups/litter (day 0)	13.7	14.9	13.3	13.6	13.3
Day 4 (precull)	13.4	14.5	13.1	13.0	12.9
Day 4 (postcull)	8.0	8.0	7.9	8.0	7.9
Day 7	8.0	8.0	7.9	8.0	7.8
Day 14	8.0	8.0	7.9	8.0	7.8
Day 21	8.0	8.0	7.9	8.0	7.7
Number of litters weaned	25	23	25	22	24
Survival indices (%)					
Gestation index	100	100	100	100	100
Viability index (d 0-4)	97	97	98	96	97
Lactation index (d 4-21)	100	100	99	100	98

Data taken from Tables 48, 52, and 53, pp. 175, 179, and 180, MRID 43864253.

TABLE 15: Viability of F_{1b} litters during lactation

Observation/ study time	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Number of litters	25	24	25	23	24
Total number of pups	392	379	397	360	382
Number of pups born alive	384	367	387	349	375
Number of pups still born	8	12	10	11	7
Sex ratio (% male)	52.6	53.4	51.4	54.7	49.9
Mean number live pups/litter (day 0)	15.4	15.3	15.5	15.2	15.6
Day 4 (precull)	14.6	14.5	15.2	14.5	15.1
Day 4 (postcull)	7.9	8.0	8.0	7.9	8.0
Day 7	7.9	8.0	7.9	7.8	7.8
Day 14	7.9	8.0	7.9	7.8	7.8
Day 21	7.8	7.9	7.8	7.8	7.7
Number of litters weaned	25	24	25	23	24
Survival indices (%)					
Gestation index	100	100	100	100	100
Viability index (d 0-4)	95	95	98	95	97
Lactation index (d 4-21)	99	99	98	99	97

Data taken from Tables 49, 55, and 56, pp. 176, 182, and 183, MRID 43864253.

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TABLE 16: Viability of F_2 litters during lactation

Observation/study time	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Number of litters	24	22	24	25	23
Total number of pups	299	277	314	327	276
Number of pups born alive	281	260	307	325	271
Number of pups still born	18	17	7	2	5
Sex ratio (% male)	51.2	54.6	44.3	55.1	52.4
Mean number live pups/litter (day 0)	11.7	11.8	12.8	13.0	11.8
Day 4 (precull)	11.3	11.2	12.1	12.4	11.3
Day 4 (postcull)	7.9	7.7	7.7	7.7	7.7
Day 7	7.9	7.6	7.5	7.6	7.7
Day 14	7.9	7.6	7.5	7.6	7.7
Day 21	7.8	7.6	7.5	7.6	7.7
Number of litters weaned	24	22	24	25	23
Survival indices (%)					
Gestation index	100	100	100	100	100
Viability index (d 0-4)	96	95	94	95	96
Lactation index (d 4-21)	99	99	98	99	99

Data taken from Tables 110, 113, and 114, pp. 237, 240, and 241, MRID 43864253.

3. Body weight

Selected body weights of the F_{1a} and F_{1b} pups during lactation are given in Table 17. F_{1a} male and female pups from the 16,000 ppm group and male pups from the 4000 ppm group had significantly ($p \leq 0.05$ or 0.01) lower body weights as compared to controls beginning on day 7 and continuing throughout lactation. F_{1a} female pups from the 4000 ppm group had significantly ($p \leq 0.01$) lower body weights than the controls on lactation days 14 and 21. Lactation day 21 body weights of male and female F_{1a} pups from the 4000 ppm litters were 88% and 90%, respectively, of the control values. High-dose F_{1a} male and female pups had lactation day 21 body weights 79% and 81%, respectively, of the control group. At 1000 ppm, males had lower body weights (95%; $p \leq 0.05$) than the controls on lactation day 21. Body weight gains in the high-dose F_{1a} males and females were significantly

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(days 1-4, $p \leq 0.05$; days 4-21, $p \leq 0.01$) less than the controls throughout lactation. The 4000 ppm group pups had significantly ($p \leq 0.01$) lower body weight gains than the controls for the intervals of lactation days 7-14, 14-21, and 4-21. At 1000 ppm, pup body weight gains were significantly ($p \leq 0.05$) less than controls on days 7-14 for males and females and on days 4-21 for males. F_{1b} generation pups from high-dose litters had significantly ($p \leq 0.05$ or 0.01) lower body weights than the controls beginning on lactation day 4 and continuing through day 21. For the 4000 ppm group, F_{1b} pup body weights were significantly less than the controls on days 14 ($p \leq 0.05$) for males and 21 ($p \leq 0.01$) for males and females. Lactation day 21 body weights of male and female F_{1b} pups from the 4000 ppm litters were 88% and 90%, respectively, of the control values. High-dose F_{1b} male and female pups had lactation day 21 body weights 77% and 78%, respectively, of the control group. Body weight gains in the high-dose F_{1b} males and females were significantly ($p \leq 0.05$ or 0.01) less than the controls throughout lactation. The 4000 ppm group pups had significantly ($p \leq 0.01$) lower body weight gains than the controls for the intervals of lactation days 7-14, 14-21, and 4-21.

Body weights for the F_2 pups during lactation are given in Table 18. Males and females from high-dose litters had significantly ($p \leq 0.01$) lower body weights than the controls on lactation days 14 and 21. At 4000 ppm, body weights were significantly lower than the controls for males ($p \leq 0.05$) and females ($p \leq 0.01$) on day 21. Lactation day 21 body weights of both male and female F_2 pups from the 4000 ppm litters were 92% of the control values. High-dose F_{1b} male and female pups had lactation day 21 body weights 82% of the control group. Body weight gains of males and females were significantly ($p \leq 0.01$) less than the control in the high-dose group for lactation day intervals 4-7, 7-14, 14-21, and 4-21 and in the 4000 ppm group on days 14-21 and 4-21.

TABLE 17: Selected group mean body weights of F_0 offspring (F_1 generation) during lactation (g)					
Day of lactation	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
F_{1a} litters					
Males					
Day 1	6.7 ± 0.52	6.5 ± 0.40	6.6 ± 0.34	6.5 ± 0.46	6.5 ± 0.44
Day 4 (postcull)	9.6 ± 0.87	9.1 ± 0.95	9.3 ± 1.04	9.2 ± 0.71	9.0 ± 0.94
Day 14	33.9 ± 1.76	31.9 ± 2.80*	32.3 ± 2.38	31.2 ± 1.81**	29.9 ± 2.15**
Day 21	55.0 ± 2.89	52.7 ± 3.89	52.4 ± 3.97*	48.6 ± 3.34**	43.6 ± 3.12**
Females					
Day 1	6.2 ± 0.59	6.2 ± 0.39	6.3 ± 0.38	6.2 ± 0.56	6.2 ± 0.45
Day 4 (postcull)	9.1 ± 0.87	8.7 ± 0.75	9.1 ± 0.84	8.9 ± 0.91	8.7 ± 1.02
Day 14	32.8 ± 1.79	31.3 ± 2.72	31.4 ± 2.49	30.6 ± 2.02**	28.9 ± 2.32**
Day 21	51.7 ± 3.61	50.2 ± 3.63	49.7 ± 3.85	46.6 ± 3.37**	41.7 ± 2.95**
F_{1b} litters					
Males					
Day 1	6.5 ± 0.62	6.5 ± 0.51	6.4 ± 0.46	6.3 ± 0.51	6.3 ± 0.40
Day 4 (postcull)	9.2 ± 1.37	9.0 ± 1.12	8.7 ± 1.04	8.6 ± 0.89	8.1 ± 1.05**
Day 14	32.3 ± 2.90	31.6 ± 3.35	30.7 ± 2.92	29.7 ± 2.83*	27.6 ± 2.87**
Day 21	53.0 ± 5.33	51.9 ± 5.44	49.8 ± 5.47	46.8 ± 4.56**	40.9 ± 4.14**
Females					
Day 1	6.2 ± 0.65	6.1 ± 0.57	6.1 ± 0.46	5.9 ± 0.44	5.9 ± 0.38
Day 4 (postcull)	8.6 ± 1.36	8.5 ± 1.26	8.3 ± 1.12	8.2 ± 0.93	7.7 ± 1.03*
Day 14	30.9 ± 3.14	30.5 ± 3.30	29.6 ± 3.04	28.9 ± 3.30	26.6 ± 2.89**
Day 21	49.9 ± 4.92	49.4 ± 5.30	47.2 ± 5.19	45.1 ± 4.63**	39.1 ± 3.72**

Data taken from Tables 57-58 and 61-62, pp. 184-185 and 188-189, respectively, MRID 43864253.

TABLE 18: Selected group mean body weights of F_1 offspring (F_2 generation) during lactation (g)					
Day of lactation	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
Males					
Day 1	6.7 ± 0.61	6.7 ± 0.67	6.6 ± 0.56	6.6 ± 0.48	6.8 ± 0.58
Day 4 (postcull)	9.9 ± 1.21	9.8 ± 1.57	9.5 ± 1.45	9.4 ± 1.22	9.6 ± 1.07
Day 14	32.5 ± 3.11	31.6 ± 4.23	32.3 ± 3.80	31.0 ± 2.15	29.5 ± 1.97**
Day 21	54.5 ± 4.63	53.7 ± 6.72	53.9 ± 6.21	50.1 ± 3.49*	44.5 ± 2.82**
Females					
Day 1	6.3 ± 0.58	6.3 ± 0.68	6.3 ± 0.54	6.3 ± 0.59	6.5 ± 0.54
Day 4 (postcull)	9.4 ± 1.11	9.3 ± 1.57	9.0 ± 1.43	8.9 ± 1.40	9.2 ± 1.13
Day 14	31.6 ± 3.10	30.6 ± 3.41	31.1 ± 3.49	29.8 ± 2.52	28.3 ± 3.37**
Day 21	51.6 ± 4.43	50.7 ± 5.27	50.8 ± 5.39	47.3 ± 3.69**	42.4 ± 4.11**

Data taken from Tables 115 and 116, pp. 242 and 243, respectively, MRID 43864253.

4. Pup physical development

The percentage of pups reaching the specified criteria for physical development is given in Table 19. For the F_{1a} pups there were no significant differences between treated and control groups in physical development as measured by pinna unfolding, auditory canal opening, or eye opening nor were any differences detected in gripping reflex, acoustic startle response, or pupillary constriction. In the F_{1b} litters, the percentage of pups with pinna unfolded by day 4 was significantly less for the 4000 and 16,000 ppm groups as compared with controls ($p \leq 0.01$ and 0.05, respectively). Eye opening was also delayed ($p \leq 0.05$) in the 4000 ppm F_{1b} pups as compared with controls. At 4000 ppm the F_2 pups had significantly ($p \leq 0.05$) delayed auditory canal opening as compared to controls.

TABLE 19: Pup physical development (%)

Endpoint	0 ppm	50 ppm	1000 ppm	4000 ppm	16,000 ppm
F_{1a} pups					
Pinna unfolding by day 4	98.7[a]	99.7	98.5	93.9	88.0
Auditory canal opening by day 13	100	98.9	100	100	99.0
Eye opening by day 15	94.5	97.8	92.1	92.0	88.3
F_{1b} pups					
Pinna unfolding by day 4	92.9	92.5	89.7	77.0**	79.5*
Auditory canal opening by day 13	99.0	99.0	94.5	97.8	93.8
Eye opening by day 15	98.0	91.1	87.5	86.4*	91.7
F_2 pups					
Pinna unfolding by day 4	100	100	100	99.3	99.0
Auditory canal opening by day 13	100	100	99.0	97.0*	99.5
Eye opening by day 15	95.3	95.5	99.2	95.0	90.2

Data taken from Table 65, 67, and 119, pp. 192, 194, and 246, respectively, MRID 43864253.
[a]Pups reaching criteria/litter.
Significantly different from control, *$p \leq 0.05$; **$p \leq 0.01$.

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4. Reevaluation of fertility

Of the F_0 parental animals, five had not shown to be fertile after mating to produce the F_{1b} litters. These included one 50 ppm female, two 4000 ppm females and one male, and one 16,000 ppm female. Upon breeding to proven control animals, pregnancy was not confirmed in one 50 ppm and one 4000 ppm female. The low-dose female was observed with vaginal prolapse 4 days after mating and was sacrificed. Histopathology revealed marked fibrosis of the uterus. The cause of infertility in the 4000 ppm female was described on histological examination as marked infiltration of polymorphs in the area of the corpus uteri. All F_1 parental animals not siring or producing an F_2 litter were proven fertile upon reevaluation of fertility.

III. DISCUSSION

Male and female Wistar rats were fed up to 16,000 ppm Reg. No. 242 009 in the diet for two generations. Two litters (F_{1a} and F_{1b}) were produced in the first generation and one litter (F_2) was produced in the second generation. At least 22 litters were produced per treatment group in each generation.

A. INVESTIGATOR'S CONCLUSIONS

The study author concluded that administration of Reg. No. 242 009 to Wistar rats over two generations resulted in systemic toxicity at dietary concentrations of 4000 ppm and 16,000 ppm. Toxicity to the parental animals was demonstrated by decreased body weights and weight gains, increased γ-glutamyltransferase, decreased fat storing cells in the liver, and reduced absolute kidney weights. The NOAEL for systemic toxicity was reported as 1000 ppm for the parental rats and their offspring.

Decreased pup weight and delays in physical development were considered to be signs of developmental toxicity and not reproductive toxicity. No impairment of reproductive function of the parental animals occurred in this study. Therefore, the study reported the NOAEL for reproductive effects to be 16,000 ppm.

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B. REVIEWER'S DISCUSSION

1. Systemic/postnatal developmental toxicity

Decreased body weights occurred in both sexes of both generations in groups given ≥4000 ppm. Although the final body weights were within 10% of the control group values, the effect was consistent throughout the study and cannot be explained by sporadic decreases in food consumption. Therefore, the effect on body weight is considered treatment-related.

The decreased kidney weights of the 4000 ppm and 16,000 ppm F_1 females and the dose-related reduction of fatty infiltration of the liver in F_0 and F_1 males are probably a result of lower body weights. The increase in γ-glutamyl transferase activity in males and females is considered treatment-related since this effect was also reported in other subchronic studies. It is interesting that liver weights were not significantly affected corresponding to the increase in enzyme activity. None of the organ effects was accompanied by gross or histopathological alterations. Statistically significant changes in alanine aminotransferase and alkaline phosphatase levels were observed at 1000 ppm and above, but were within the normal range of values, and again, were not accompanied by histopathological changes. Therefore toxicological significance was not established.

Pup body weights in both generations were significantly reduced during lactation in groups receiving ≥4000 ppm. The reduction in pup body weights became most pronounced after day 14 of lactation when it would be expected that the pups were starting to eat the treated diets. Therefore, the effect on pup body weight is considered directly related to the test material. Concurrent with the decreased growth of the pups, delayed physical development was measured as delays in pinna unfolding, eye opening, and auditory canal opening. Fetal body weights were not affected in a standard developmental toxicity study (MRID 43864251) during which rats were given Reg. No. 242 009 at a limit dose of 1000 mg/kg/day on gestation days 6-15. This is consistent with the current study in which pup body weights were most affected after they started eating the test article.

Therefore, the LOEL for systemic/postnatal developmental toxicity is 4000 ppm based on reduced body weights and body weight gains of F_0 and F_1

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parental animals and reduced growth of the F_1 and F_2 pups. The systemic/postnatal developmental toxicity NOEL is 1000 ppm.

2. Reproductive toxicity

There were no dose- or treatment-related effects on the reproductive performance or pup survival of either generation. The low fertility index for the 4000 ppm F_0 males for production of the F_{1a} litters was not repeated with the F_{1b} litters or in the treated F_1 males with production of the F_2 litters. Also, all animals not producing a litter were proven fertile upon reevaluation with the exception of two F_0 females. Histopathological examination of these two revealed changes in the uteri that are considered unrelated to treatment. Therefore, this effect in the F_0 males is considered incidental to treatment with Reg. No. 242 009.

Therefore, the NOEL for reproductive toxicity is ≥16,000 ppm and the corresponding LOEL for reproductive toxicity was not identified.

C. STUDY DEFICIENCIES

There were no deficiencies in the conduct of this study.

D. CORE CLASSIFICATION

This study is classified as Acceptable and satisfies the guideline requirement for a reproduction study (83-4) in rats.